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(54) Title: CALIBRATION SOLUTIONS USEFUL FOR ANALYSES OF BIOLOGICAL FLUIDS AND METHODS EMPLOYING SAME

(57) Abstract

Novel calibration solutions are provided which are useful, for example, with sensor assemblies used for analysis of CO₂, and optionally, for concurrent analysis of O₂, especially in combination infusion fluid delivery/blood chemistry analysis systems which include a sensor assembly with each of the assembly electrodes mounted in an electrode cavity in the assembly. The analysis system used in the practice of the present invention typically includes provision for delivering infusion fluid and measuring blood chemistry during reinfusion of the physiological fluid at approximately the same flow rates. The invention calibration solutions are useful for calibrating an array of sensors capable of simultaneously measuring a number of blood chemistry parameters, including the partial pressures (tensions) of carbon dioxide and oxygen, pH (hydrogen ion), sodium, potassium, ionized calcium, ionized magnesium, chloride, glucose, lactate and hematocrit, in body fluids. More particularly, this invention relates to the use of an infusible intravenous solution to facilitate calibration on a regular basis for every individual sensor in a sensor assembly, which is in constant fluid communication with the body regardless of whether the sensors are *ex vivo* or *in vivo*.

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CALIBRATION SOLUTIONS USEFUL FOR ANALYSES OF
BIOLOGICAL FLUIDS AND METHODS EMPLOYING SAME

This application is a continuation-in-part of United States Serial No. 07/937,980, filed August 28, 1992, now pending.

This invention relates to the diagnostic

5 testing of body fluids, typically in conjunction with the infusion of fluids. In a particular aspect, the invention relates to calibration solutions useful with low-cost, disposable, sensor assemblies used in automated bedside monitors.

10

BACKGROUND OF THE INVENTION

Low-cost, disposable, electrochemical electrode assemblies have special utility as part of infusion fluid delivery systems commonly used in hospital patient care. Such systems infuse nutrients, medications, and the like

15 directly into the patient at a controlled rate and in precise quantities for maximum effectiveness. Infusion fluid delivery systems are connected to a patient at an intravenous (IV) port, in which a hollow needle/catheter combination is inserted into a blood vessel of the

20 patient and thereafter an infusion fluid is introduced into the vessel at a controlled rate, typically using a peristaltic pump. Blood chemistry monitoring systems that are combined with infusion delivery systems of this kind use the IV port to periodically withdraw a blood

25 sample, perform measurements of blood ion concentrations and the like, and then discard the blood or reinfuse it into the patient. The system then resumes delivery of the infusion fluid.

Such combined infusion fluid delivery and blood

30 chemistry monitoring systems include an infusion line and catheter through which the infusion fluid is provided to

the patient and blood samples are withdrawn. The infusion line incorporates an electrode assembly having electrochemical sensors that are periodically exposed to the blood samples and thereby provide electrical signals 5 to an analyzer for conversion into corresponding blood chemistry data. A control unit periodically halts delivery of the infusion fluid for a brief interval, during which time a blood sample is withdrawn from the patient into the infusion line and routed to the 10 electrode assembly, which then generates the electrical signals. After the electrical signals have been received by the analyzer, the control unit disposes of the blood or reinfuses the blood sample into the patient, and the flow of infusion fluid is resumed.

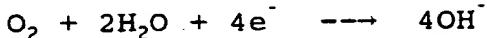
15 The electrode assembly typically, among other types of electrochemical sensors, includes a reference electrode and a plurality of sensing electrodes (sensors) that are each sensitive to a particular ion or species of interest. All of the electrodes are typically embedded 20 in the base of the electrode assembly. For example, ion-sensitive electrodes (ISE) generate electrical signals only in response to contact with the particular ion to which they are sensitive, and therefore provide selective measurement of the amount of that ion in the 25 blood. This type of sensing electrode can be provided to measure, for example, blood calcium, hydrogen ion, chloride, potassium, and sodium. In a differential measurement system, the reference electrode might be another ion-selective electrode (e.g., a chloride or 30 sodium electrode) that is continuously exposed to a calibration or reference fluid. Alternatively, in a non-differential measurement system, a conventional reference electrode (which maintains a fixed potential when exposed either to reference fluid or to analyte) is 35 required.

In a differential measurement system, during the delivery of calibration fluid, the calibration fluid flows past both the reference electrode and the sensing electrodes, and the electrical potential between the 5 reference electrode and each sensing electrode is measured. This provides a calibration measurement of the electrode assembly. During a subsequent blood chemistry measurement, a blood sample is drawn into the electrode assembly, where it comes into contact with the sensing 10 electrodes, but not the reference electrode. The electrical potential between the reference electrode and each sensing electrode is measured again and compared with the earlier calibration measurement to provide an indication of the ion concentration in the blood of the 15 particular ion to which the sensing electrode is sensitive. After measurement is completed, the blood sample is discarded or reinfused from the electrode assembly back into the patient, and delivery of infusion fluid is resumed.

20 Presently employed electrochemical sensors for clinical diagnostic applications can be divided into three categories: potentiometric, amperometric and ac impedance. For example, hematocrit (Hct), which is defined as the volume percent of red cells in the blood, 25 can be determined by measuring the ac impedance of the blood with a pair of metal electrodes, typically at 1 kilohertz (kHz).

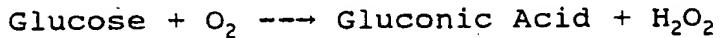
An amperometric sensor correlates the concentration of a specific component of interest to a 30 current output. Typically, oxygen partial pressure (pO_2) and glucose (Glu) are determined with amperometric sensors. An oxygen sensor assembly usually consists of a noble metal (e.g., platinum or gold) working electrode and a suitable counter electrode (e.g., silver/silver 35 chloride). An oxygen permeable, but liquid impermeable,

membrane is usually mounted over the sensor assembly to separate the sample from the internal electrolyte to avoid contamination. The sensor measures the limiting current of oxygen reduction at the working electrode 5 according to the following equation:



This is accomplished by applying a bias voltage of approximately 700 mV between the working (negative) electrode and the counter (positive) electrode. This is 10 also known as a Clark electrode. The current passing between these two electrodes is proportional to the pO_2 level in the sample.

The glucose sensor is very similar in construction to an oxygen sensor. The difference is that 15 a hydrophilic membrane with immobilized glucose oxidase is used instead of the hydrophobic oxygen membrane. In the presence of glucose oxidase (GOD), the following reaction takes place:



20 In this case, glucose concentration can be determined by either polarizing the working electrode anodically or cathodically by approximately 700 mV to measure the rate of hydrogen peroxide oxidation or oxygen reduction, respectively.

25 A potentiometric sensor provides a voltage change which is related to the species of interest. Ionic species, such as hydrogen ion (H^+), sodium (Na^+), potassium (K^+), ionized calcium (Ca^{++}) and chloride (Cl^-), are commonly measured by ion selective electrodes (ISE), 30 a typical class of potentiometric sensors. The commonly used CO_2 sensor, better known as the Severinghaus electrode, is also a potentiometric sensor (and is, in

fact, essentially a modified pH sensor). Typically, it consists of a pH electrode and a reference electrode with both covered by a hydrophobic (gas permeable-liquid impermeable) membrane such as silicone. There is a thin 5 layer of weakly buffered internal electrolyte (e.g., 0.001 M NaHCO₃) between the hydrophobic membrane and the pH sensing membrane. Carbon dioxide in the sample eventually reaches equilibrium with the internal electrolyte and produces a pH shift as a result of the 10 following equation:



The resulting pH shift is then measured by the pH electrode. Therefore, there is a direct relationship between the CO₂ partial pressure (pCO₂) in a sample and 15 the pH thereof.

The accuracy of measurement obtained with any of the above-described sensors can be adversely affected by drift, particularly after exposure to biological fluids such as whole blood. Therefore, frequent 20 calibration is required. This is particularly true for gases such as pO₂ and pCO₂ because any change in the gas transport properties of the membrane may affect the sensor output. To this end, a number of calibration fluids are usually needed. This is because at least two 25 different calibrant concentration levels are usually required to characterize a sensor. For a multi-parameter system, it is sometimes not possible to use the same two solutions to calibrate all sensors due to concerns such as chemical incompatibility and long term stability. 30 Moreover, since it is technically very difficult to maintain pCO₂ and pO₂ constant at desired calibration levels, most conventional blood chemistry analyzers carry two gas cylinders and several bottles of reagents just to fulfill the calibration requirements. This makes the 35 system bulky and cumbersome to use.

An attempt was made to fill pre-tonometered liquid calibrants sealed into aluminum foil pouches under partial vacuum as calibrants, as described by Burleigh (U.S. Patent 4,734,184). This approach substantially 5 reduced the size, and improved the portability of blood chemistry analyzers. However, the contents of the pouch have a limited life once the pouch is opened.

The current trend is to move away from bench top analyzers towards the use of bedside analytical 10 systems. Moreover, instead of taking samples from the patients, sensors are either miniaturized and inserted into a blood vessel (*in vivo*) or constructed as part of a flow cell connected to the patient end of an existing vascular access port (*ex vivo*) to provide continuous 15 monitoring of blood chemistry.

The *in vivo* approach is conceptually more attractive because it provides continuous results without intervention. However, it is much more difficult to implement in practice. The major hurdle is, of course, 20 the blood clotting problem. Blood compatibility has always been a challenging issue. Even with a short term solution in hand, once sensors are placed in the blood stream, repeated calibration becomes very difficult.

The *ex vivo* approach, originally described by 25 Parker (U.S. Patent No. 4,573,968), employs a control unit to periodically withdraw a small amount of blood to come in contact with sensors (which are incorporated into an in-line flow cell) when a reading is desired. After a measurement is taken, the control unit resumes delivering 30 physiological saline into the blood vessel. As a result, the blood drawn is effectively flushed back into the patient and the sensors are washed clean. Kater (in U.S. Patent No. 4,535,786) discloses a method to use an infusible intravenous (I.V.) saline solution to calibrate

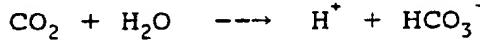
ionic species in the biological fluid. However, Kater does not address the calibration of species such as glucose, pO_2 , and pCO_2 , as contemplated by the present invention.

5 As previously indicated, all blood chemistry sensors require frequent calibration in order to maintain the accuracy of measurement. In a multi-parameter bench top analyzer system, it often requires more than one calibration fluid (and/or gas) to accomplish this task.

10 In an *ex vivo* blood chemistry monitor, it is much more desirable to use a single calibration solution for all the sensors, and to flush the sensors clean. In a multi-parameter *ex vivo* system, such as the VIA 1-01 Blood Chemistry Monitor (available from Via Medical

15 Corporation, San Diego, CA), i.e., a system that measures one or more of Na^+ , K^+ , Ca^{++} , Mg^{++} , pH, pCO_2 , pO_2 , glucose, lactate and hematocrit, this requirement becomes very demanding.

In particular, the calibration of pH and pCO_2 20 remains a challenge. In an aqueous solution, these two parameters are inter-related by the following equation:



At 37°C, the pH in a simple bicarbonate-containing solution is equal to

25
$$6.10 + \log \{[HCO_3^-]/0.0301 pCO_2\}$$

Since the normal pCO_2 in arterial blood is approximately 40 mmHg, while the atmosphere contains 0.2 - 0.5 mmHg of CO_2 , atmospheric CO_2 levels are not only too low, but they are also too variable to serve as a calibration point.

30 Hence, an external CO_2 source is required. Normally, the approach used in the art is to tonometer the solution

with a known CO₂-containing gas, and then package the gas-equilibrated solution in a sealed container. This is not only costly but also requires considerable effort to demonstrate its safety as an infusible solution.

5 Although U. S. Patent No. 4,736,748 (Nakamura) suggests that simultaneous calibration for Na⁺, K⁺, Ca⁺⁺, glucose and hematocrit, can be carried out with Ringer's Lactate having glucose added thereto, such a solution could not possibly be used for pH, pCO₂ and/or pO₂.

10 calibration because the solution has no well defined pH value or pO₂ value, and contains essentially no CO₂. Indeed, since the amount of oxygen dissolved in Lactated Ringer's solution is not fixed (being a function of ambient temperature and barometric pressure--parameters

15 which Nakamura does not contemplate monitoring), the reference does not teach how to use Lactated Ringer's solution as an oxygen calibrant. Moreover, the oxygen partial pressure in physiological saline is substantially higher than that in blood. It would be desirable for a

20 calibration solution to have oxygen levels which are relatively close to physiological levels, regardless of what type of sensor is employed. Furthermore, Nakamura does not address measurement of hematocrit levels at all.

25 While Burleigh, supra.., describes a solution which can be used for calibration of CO₂, the reference does not contemplate the use of an infusible calibrant, much less a substantially non-buffered, infusible calibrant. Indeed, the Burleigh CO₂ calibration solution would not be acceptable for infusion. In contrast to the

30 practice of the present invention, after sample analysis, Burleigh directs assayed fluids into a waste collection reservoir. In accordance with the present invention, a very different analytical system is contemplated wherein sample withdrawn from a subject is reinfused after

35 analysis. Thus, a different calibration solution is

required for the practice of the present invention relative to what is taught in the art. Since Burleigh does not contemplate a substantially non-buffered, infusible calibrant, the reference provides no guidance 5 as to suitable calibration solutions for use with combined infusion fluid delivery/blood chemistry measurement systems, as contemplated herein.

Sone et al., U.S. 5,132,000 (1992) is similar to Burleigh in that the reference describes solutions 10 which can be used for calibration of CO₂-containing solutions. The reference does not, however, contemplate the use of an infusible calibrant. Similar to Burleigh, the Sone calibration solutions would not be acceptable for infusion. Successful analysis according to the Sone 15 teaching requires the use of strong pH buffering. The level of buffering and ionic strength required by Sone clearly makes such solutions unacceptable for infusion.

From the discussion above, it should be apparent that there is a need for calibration solutions 20 useful, for example, in combined infusion fluid delivery and blood chemistry measurement systems that allow accurate, reliable measurements of blood chemistry, that avoid the need for multiple calibration and/or reference solutions, and that are relatively easy to prepare by 25 mixing injectable media that are readily available for patient use as "off-the-shelf" items. The present invention satisfies these needs.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there 30 are provided methods for the assay of CO₂ partial pressure (pCO₂), and optionally, O₂ partial pressure (pO₂), in physiological fluids. In addition, there are provided methods for the calibration of sensors employed for the

detection of pCO_2 , and optionally, pO_2 . Further, there are provided calibration solutions suitable for use in the above methods. Presently preferred calibration solutions employed in the practice of the present 5 invention include components necessary for the calibration of systems employed for the essentially simultaneous measurement of one or more of sodium ion concentration, potassium ion concentration, calcium ion concentration, magnesium ion concentration, hydrogen ion 10 concentration, glucose concentrations, lactate concentrations, chloride concentrations, and hematocrit levels, in addition to carbon dioxide (and optionally, oxygen) partial pressures.

The invention provides simple means to prepare 15 infusible calibration solutions, thereby eliminating the need for multiple calibration solutions, and increasing the measurement accuracy of blood chemistry analyses. In addition, the present invention provides improved assays employing the above-described infusible calibration 20 solutions.

Other features and advantages of the present invention should be apparent from the following detailed description, which illustrates, by way of example, the principles of the invention.

25

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram of a combination infusion fluid delivery and blood chemistry analysis system useful in the practice of the present invention.

FIG. 2 is a plan view of a reference/sensor 30 electrode assembly useful in the practice of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a method for the assay of CO_2 partial pressure (pCO_2), and optionally, O_2 partial pressure (pO_2), in 5 physiological fluid, said method comprising
contacting an assembly having:
a fluid passageway and a sensor for pCO_2 , and optionally a sensor for pO_2 , exposed to said fluid passageway, and
10 means to pass physiological fluid and/or calibrant over said sensor,
with an infusion medium/calibrant comprising:
physiological sodium chloride-containing saline, and
15 an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg; and calibrating said CO_2 sensor (and optionally, said pO_2 sensor); and thereafter
20 contacting said assembly with said physiological fluid and measuring the CO_2 partial pressure (and optionally the O_2 partial pressure) in said physiological fluid.

Physiological fluids contemplated for analysis in accordance with the present invention include whole 30 blood, blood plasma, blood serum, urine, dialysate, and the like.

"Suitable carbon dioxide sources" contemplated for use in the practice of the present invention are compounds which produce carbon dioxide upon introduction

into an infusible saline solution. Examples of suitable carbon dioxide sources include sodium carbonate, sodium bicarbonate, calcium carbonate, ascorbic acid, ascorbate, and derivatives thereof, such as, for example, the the 5 ascorbic acid derivatives described by Satoh et al., in U.S. Patent No. 5,194,445, incorporated by reference herein.

Sensor assemblies contemplated for use in the practice of the present invention include indwelling 10 (i.e., intravascular) catheter-based fiber optical blood gas sensors (such as are available from Puritan-Bennett, Optex, Biomedical Sensors, and the like); extracorporeal blood gas sensors (such as are available from 3M/CDI, Biomedical Sensors, Mallinckrodt, and the like); etc, as 15 well as the sensor assembly shown in FIG. 2.

Calibrants contemplated for use in the practice of the present invention are typically non-buffered solutions, or, if buffered, weakly buffered so as not to preclude the use of invention calibrants as infusion 20 medium. Such calibrants include:

physiological sodium chloride-containing saline, further containing an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and 25 optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg, optionally containing one or more additional electrolytes,

0.9% sodium chloride containing an amount of a suitable carbon dioxide source effective to provide a 30 stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg, optionally containing one or more additional electrolytes,

5 Isolyte™ brand infusible injection solution (available from Kendall McGaw, Irvine, California) containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

10 PlasmaLyte™ brand infusible injection solution (available from Baxter Healthcare Corporation, Chicago, Illinois) containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

15 Ringer's injection containing an amount a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

20 Ringer's Acetate containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

25 Ringer's Lactate containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

30 and the like.

The pCO₂, pO₂ and pH levels of several of the above-described calibration/injection solutions are summarized below:

14

	<u>Composition</u>	<u>pCO₂ (37°C) (mm Hg)</u>	<u>pO₂ (37°C) (mm Hg)</u>	<u>pH (37°C)</u>
	Lactated Ringer's	0.2-0.6	185	6.20 ± 0.5
5	Lactated Ringer's with 20 mM/L NaHCO ₃	8.0	185	8.05
	Lactated Ringer's with 20 mM/L NaHCO ₃ and 0.05 mM/L EDTA	9.0	185	7.95
10	Lactated Ringer's with 20 mM/L NaHCO ₃ , 1 mM/L Na ₂ HPO ₄ and 2 mM/L NaH ₂ PO ₄	55	185	7.10
15	Lactated Ringer's containing 5% L-ascorbic acid	7-10	0-5	6.0
	Lactated Ringer's containing 5% L-ascorbate	40	0-5	8.0

20 Sodium bicarbonate injection solutions useful
in the invention process are readily available, typically
at 8.4 w/w %, 7 w/w %, or 4.2 w/w %. Sodium bicarbonate
injection solutions may also optionally contain
stabilizing agent(s), which may act as pH regulating
25 agents as well. The presence of stabilizing agents is
frequently desirable because the pCO₂ level of an
injection solution is a function of the pH of the
injection solution, as well as the HCO₃⁻ concentration
used.

30 Ascorbic acid (or ascorbate) injection
solutions useful in the invention process are readily
available, typically at 10-50 w/w %; for example,
Cevalin™, available from Eli Lilly & Co., is provided as
an ascorbate solution containing 10-50 w/w % ascorbate,
35 or Cenolate™, available from Abbott Laboratories, Inc., is
provided as a 10 w/w % ascorbate-containing solution.
Ascorbic acid injection solutions may also optionally
contain pH regulating agents.

Electrolyte injections such as Ringer's Injection, Ringer's Acetate, and Ringer's Lactate contain fixed levels of Na^+ , Cl^- , K^+ and Ca^{++} and can be readily used to calibrate the corresponding sensors. Although 5 I.V. saline solutions with dextrose are widely used in hospitals, most pre-mixed dextrose-containing I.V. solutions are 20-100 times too concentrated for use as a calibrant for blood glucose measurement. Fortunately, 10 sterile dextrose injection solutions (typically 10 w/w % or higher) are widely available. A small amount of such 15 an injection can be added to Ringer's Lactate (e.g., 10 ml of 10 w/w % dextrose per 1,000 ml) to provide a calibration point closer to the normal blood glucose level (i.e., 100 milligram per deciliter).

15 Since hematocrit is an ac impedance measurement, in principle, it only requires a single calibration point to establish the constant of the conductivity cell. This can easily be done with glucose-containing Ringer's Lactate since its conductivity is 20 fixed as long as the temperature is known.

As for pO_2 , since Ringer's Lactate is generally in equilibrium with the atmosphere at ambient temperature in most clinical settings, the amount of dissolved oxygen can be derived if the temperature and barometric pressure 25 are available. This can readily be accomplished by one of skill in the art. Alternatively, an oxygen scavenger such as ascorbic acid can be employed to decrease or deplete the oxygen tension of a given solution. The oxygen tension in a situation where an oxygen scavenger 30 has been added can readily be determined by reference to a calibration curve, or a sufficient amount of oxygen scavenger can be employed to ensure substantially complete removal of oxygen from the solution, i.e., pO_2 approaches zero.

In accordance with the present invention, it has been found, for example, that adding a small amount of sodium bicarbonate (i.e., 10 ml of 8.4% NaHCO_3) to a 500 ml bag of Ringer's Lactate could stabilize the pH and 5 pCO_2 thereof for many hours (up to about 18 hours or longer) at pH = 7.95 and pCO_2 = 9 mm Hg (when the pH and pCO_2 is measured at 37°C). By adding other pH regulating agents, such as for example, sodium or potassium phosphate, to lower the pH to approximately 7.10, it 10 would be possible to maintain the pCO_2 level at above 55 mm Hg.

Furthermore, the addition of a suitable CO_2 source (such as sodium bicarbonate) to injection solutions, such as Ringer's Lactate, does not 15 significantly affect other parameters, for at least several days. Therefore, it is possible to use such a fluid to calibrate the entire multi-sensor array. The invention calibration solutions, therefore, make it possible to have a single infusible liquid calibrant for 20 combinations of one or more of Na^+ , Cl^- , K^+ , Ca^{++} , Mg^{++} , pH, pO_2 , glucose, lactate and pH sensors, in addition to pCO_2 .

Those of skill in the art recognize that a variety of optional components can be included in the calibration solutions employed in the practice of the 25 present invention. For example, in the range of about 10 up to 10,000 mg/L of dextrose can be included as a calibrant for glucose. It is also frequently desirable to include in the range of about 10 up to 50,000 IU/L sodium heparin in the infusion medium/calibrant. It is 30 also frequently desirable to include pH regulating reagents in the infusion medium/calibrant. Exemplary pH regulating reagents include sodium or potassium phosphates, sodium or potassium acetates, sodium or potassium citrates, EDTA (ethylenediaminetetraacetic acid), and the like.

The pH, pCO_2 and pO_2 levels of calibration solutions employed in the practice of the present invention remain more or less constant in the I.V. bag because the plastic bag materials from which I. V. bags 5 are constructed are generally relatively gas impermeable. However, the I. V. solution administration set, particularly the peristaltic pumping segment, may not be as gas-tight. As the solution travels along the I. V. line towards the sensors and the vascular access port, 10 some CO_2 will likely be lost, and O_2 will tend to equilibrate with ambient pO_2 , especially when the fluid sits almost stagnant over the sensors (for example, when the monitor is in standby mode). This problem can readily be addressed in a variety of ways, for example, 15 by taking advantage of the fluid handling capability of the infusion system. Periodically, a certain amount of solution (e.g., 5 ml) may be pumped into the patient in order to bring fresh solution from the bag to the sensors for calibration.

20 However, it may be impractical, or clinically undesirable, to infuse large amounts of I.V. fluids into a patient over a given period of time, especially for neonates, infants, fluid-restricted patients, and the like. An alternative means to compensate for small 25 changes in calibrant pCO_2 levels (as a result of CO_2 leakage, temperature fluctuations, and the like) is based on the fact that for a given HCO_3^- -containing I.V. solution, the relation between pH and CO_2 is well defined. For example, as presented above, the pH of a simple 30 bicarbonate-containing solution at 37°C is

$$6.10 + \log \{[\text{HCO}_3^-]/0.0301 \text{ pCO}_2\}$$

In an aqueous solution containing other compounds (e.g., sodium, potassium, calcium, magnesium, chloride, glucose, and the like), it is still possible to model the

relationship between pH and pCO_2 (based on the above theoretical relationship), and experimentally verify the results. Thus, small fluctuations in pCO_2 in calibrant which is in contact with the pCO_2 sensor may be corrected 5 by monitoring the pH on a continuous basis. This can be accomplished, for example, using the pH sensor in sensor assembly 12 (shown in FIG. 2). However, because the pH sensor in sensor assembly 12 is periodically exposed to physiological fluid, it may drift slightly over time, due 10 primarily to the possibility of the buildup of a thin protein layer thereon. Accordingly, it is presently preferred to use a separate pH sensor (which is constantly exposed to calibrant only) to provide much more reliable results. To this end, electrode 39 in 15 reference assembly 14, as shown in FIG. 2, is provided as a pH sensor specifically for this purpose. Observed changes in pH can then be used to correct the calibration points for pH and pCO_2 for the measurements taken shortly thereafter.

20 Oxygen partial pressure can readily be determined by reference to a calibration curve. Thus, as noted above, the pO_2 of physiological saline is substantially higher than typical blood oxygen levels. Addition of an oxygen scavenger, such as ascorbic acid, 25 ascorbate, and derivatives thereof, would reduce oxygen levels substantially, to levels much more in the range of normal physiological values. The pO_2 for a given blood sample can readily be determined by reference to a calibration curve, or a sufficient amount of oxygen 30 scavenger can be employed to ensure substantially complete removal of oxygen from the solution.

 In accordance with another embodiment of the present invention, there are provided physiological saline solutions suitable for infusion into a subject, 35 and simultaneously suitable for calibration of sensors

In accordance with a presently preferred embodiment of the present invention, a single infusible calibrant is employed which enables the substantially simultaneous calibration of a multi-sensor assembly comprising a plurality of sensors, wherein the plurality of sensors are responsive to one or more additional species selected from Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^- , pH, glucose and lactate, in addition to pCO_2 (and optionally pO_2).
Multi-sensor assemblies capable of detecting (i.e., responsive to) two or more of the above-identified species have been developed for use in association with suitable ex vivo blood chemistry monitors.

In accordance with another embodiment of the
25 present invention, there is provided an improved
combination infusion delivery system and chemical
analysis system having a sensor capable of determining CO₂
partial pressure, and optionally, a sensor capable of
determining O₂ partial pressure, in physiological fluid,
30 wherein physiological saline is employed as the infusion
medium, the improvement comprising introducing an amount
of a suitable carbon dioxide source into said
physiological saline effective to provide a stable CO₂
partial pressure and optionally a stable O₂ partial
35 pressure adequate to calibrate said CO₂ and said O₂

sensor. Typically, an effective amount of a suitable carbon dioxide source is an amount effective to provide a stable pCO_2 in the range of about 1 up to 100 mm Hg, and a stable pO_2 in the range of about 0 up to 200 mm Hg in said 5 physiological saline solution.

In accordance with yet another embodiment of the present invention, there is provided a method for the calibration of a sensor employed for the detection of CO_2 partial pressure, and optionally, O_2 partial pressure, in 10 physiological fluid, said method comprising contacting a sensor assembly having:

15 a fluid passageway and a sensor for CO_2 , and optionally a sensor for O_2 , exposed to said fluid passageway, and means to pass physiological fluid and/or calibrant over said sensor, with an infusion medium/calibrant comprising: physiological sodium chloride-containing aqueous saline, and 20 an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg; and thereafter 25 calibrating said sensor.

Control system(s) employed in the practice of the present invention preferably control the flow of 30 fluids so that infusion fluid is used for calibration and, during calibration, is made to flow at a predetermined flow rate through the electrode assembly. When blood is drawn up into the infusion line, it is made to flow past the sensing electrode during measurement at 35 substantially the same predetermined flow rate as during

calibration. This eliminates any effect fluid flow rate might otherwise have on the measurements. Further, the electrode assembly can be used for both a reference assembly having a reference electrode and a sensor 5 assembly having one or more sensing electrodes, with the reference assembly and sensor assembly mounted side-by-side in a compact unit that is easy to remove and replace.

The infusion/analysis system employed in 10 accordance with the present invention calibrates during infusion and takes measurements of blood chemistry during the time that fluid sample drawn into the infusion line is being reinfused into the patient.

The reference electrode and sensing electrodes 15 can be provided in separate assemblies for a blood chemistry measurement system, placed side-by-side in a compact unit. Placing the reference and sensor assemblies in a single unit provides an assembly that is more comfortable for the patient, facilitates removal and 20 replacement of the assemblies, and also allows more precise calibration of the blood volume withdrawn and fluid infused, providing increased accuracy and reliability. For example, the time needed for the desired amount of blood to be withdrawn into the sensor 25 assembly can be calculated and an error condition can be signalled if this time is exceeded with no indication of blood in the assembly. The diameter of the infusion line between the assemblies can be enlarged, reducing the electrical resistance of the fluid between the assemblies 30 and providing more accurate readings.

A temperature sensing electrode (e.g., a thermistor or thermal couple) can be provided with the sensing electrodes, to provide a temperature signal that can be used to correct the sensed readings to compensate

for changes in temperature. Furthermore, an additional electrode can be provided to act as a key to the controller to signal what particular types of sensors are provided in the assembly. For example, standardized 5 groupings of sensors can be provided, and the keying electrode can cause the controller to act appropriately for the group of sensors provided.

In a presently preferred embodiment of the present invention, the combination infusion fluid 10 delivery system and blood chemistry analysis system illustrated in FIG. 1 is employed. System 10 of FIG. 1 includes a sensor assembly 12 and a reference assembly 14 having electrodes constructed as described in United States Patent Application Serial No. 07/581,803, filed 15, September 13, 1990, issued as United States Patent No. 5,165,406 (Nov. 24, 1992), the two assemblies being mounted side-by-side on an arm board 16 that is attached to a patient 18. While the assembly includes a separate sensor assembly and reference assembly, and therefore is 20 suited to a differential measurement system, it is to be understood that the assemblies could be integrated into a single unit to operate in a non-differential measurement system. The sensor assembly 12 is connected to the patient via an intravenous (IV) port 20 and an infusion 25 line 22, which continues upstream of the sensor assembly to the reference assembly 14 and then to a peristaltic pump 24 that is controlled by a control unit 26. Those skilled in the art will appreciate that the pump and control unit can alternatively be integrated into a 30 single unit. Finally, the infusion line 22 continues upstream of the pump to an infusion fluid source 28.

During calibration of system 10, control unit 26 controls pump 24 and meters infusion fluid from the infusion fluid source 28, through the pump, past 35 reference assembly 14, past sensor assembly 12, and into

the patient 18. The reference and sensor assemblies preferably include electrodes constructed as described in United States Patent No. 5,165,406, and during calibration, the electrical potential between respective 5 electrodes of the two assemblies is measured to provide a series of calibration measurements for system 10.

During a measurement mode of the system, blood is withdrawn from the patient 18 into infusion line 22 past sensor assembly 12 but not up to reference assembly 10 14, as described further below, and the electrical potential between respective electrodes is again measured. The electrical potential will be changed from the calibration measurements, and the difference corresponds to a calculated amount of a particular ion in 15 the patient's blood. Sensor assembly 12 can include, for example, sensors that are sensitive to blood chemistry ions including calcium, hydrogen, chloride, potassium, sodium, CO₂ partial pressure, O₂ partial pressure, and the like.

20 Substantially the same flow rates are used in the infusion line through the electrode assembly when infusion fluid flows during calibration as when blood flows during measurement. More particularly, the control system controls the infusion pump of the combined 25 infusion fluid delivery and blood chemistry measurement system such that the infusion fluid is pumped past the reference and sensor electrodes at a fixed flow rate during calibration, and the blood measurement is taken while the blood is infused back into the patient at 30 approximately the same flow rate.

As shown in FIG. 2, the sensor electrode assembly 12 and the reference electrode assembly 14 contain electrodes that are constructed in accordance with the present invention. The assemblies are in flow

communication via a connecting conduit 30 in the infusion line 22. The sensors in the sensor assembly have one or more sensing electrodes (illustrated in the Figure with four sensors, i.e., 32a, 32b, 32c, and 32d). Each sensor 5 reacts with fluid in the assembly and generates a voltage signal relative to the reference assembly 14. Those of skill in the art recognize that the number of sensing electrodes included in the sensor assembly can vary widely. Thus, in the range of one up to ten sensors or 10 more can be employed in the practice of the present invention. One of the reference assembly's electrodes 34 is used as patient or solution ground, and are connected to what is known as an isolated ground (not illustrated). A second reference electrode 36 is a common reference for 15 the sensor electrodes. That is, the sensor electrode electrical signals are with respect to the common reference, thereby providing differential measurement.

A temperature sensing line 38 is provided from a built-in thermistor (located in sensor assembly 12) to 20 the control unit 26. The temperature sensing line provides the control unit with a signal that represents the temperature of the calibration fluid. This information is used to calibrate the output signals from the electrodes to give more accurate blood chemistry 25 readings. Finally, a third electrode 39 is a pH sensor which is dedicated to monitoring the pH of the calibrant on a continuous basis. Any changes in pH detected will be used to correct the pH and pCO₂ calibration points.

Presently preferred electrode assemblies useful 30 in the practice of the present invention are described in United States Patent No. 5,165,406.

The combination infusion fluid delivery system and blood chemistry analysis system of FIG. 1 referred to previously includes the sensor assembly 12 having various

electrodes sensitive to particular blood chemistry ions, such as calcium, hydrogen, chloride, potassium, sodium, and the like, and is preferably constructed in accordance with the assembly described in United States Patent No.

5 5,165,406. As shown in FIGS. 1 and 2, the sensor assembly 12 and reference assembly 14 are in flow communication, separated by a connecting loop 30 of the infusion line 22 that is approximately four to six inches in length. The connecting loop advantageously has a
10 larger internal diameter than the remainder of the infusion line 22. The larger diameter facilitates cleaning the line of bubbles and reduces the electrical resistance of the fluid between the electrodes. The reduced resistance increases the accuracy of measurement.

15 During the measurement mode of operation, the delivery of infusion fluid from the infusion fluid source 28 into the patient is halted. The direction of flow of the infusion fluid in line 22 is then reversed. That is, infusion fluid in the line is pumped back into the fluid source. This process eventually withdraws blood from the patient into infusion line 22 past sensor assembly 12 and into connecting loop 30, but not far enough to reach the
20 level of reference assembly 14. This is a volume of approximately 0.5-1.0 cc of blood.

25 After the blood is drawn into line 22, it remains in place for approximately 15 to 20 seconds while the system stabilizes. During this period, the blood in the infusion line is reinfused into the patient 18 under control of control unit 26 at approximately the same rate
30 as that at which the infusion fluid was earlier delivered into the patient during calibration. After a short time interval of reinfusion, for stabilization of the sensors, the potential differences between the respective electrodes of reference assembly 14 and sensor assembly
35 12 are measured and provided to control unit 26. Making

the blood chemistry measurements at a blood flow rate equal to that of the earlier calibrating flow rate eliminates any effect on the measurements that the fluid flow might otherwise have. This yields an accurate 5 reading of the blood chemistry parameters.

The sensor assembly may be thermostatted at about 37°C (for example, by being positioned inside an electrically heated enclosure). Any deviation from the target temperature of 37°C will be detected by 10 temperature sensing line 38. Temperature sensing line 38 provides control unit 26 with an indication of the temperature at which the analytical measurement is carried out. The measured electrical potential from the various electrodes will change with temperature such that 15 temperature changes in calibration fluid from the time of calibration to the time of measurement can provide inaccurate data. Therefore, the control unit can use the temperature information to adjust the blood chemistry readings to compensate for the changes in temperature, 20 providing increased accuracy and reliability. In addition, the temperature information provided by sensor 38 can also be used as part of a feedback control system for control of the heater used to heat the sensor assembly.

25 Eventually, after the blood chemistry measurements have been completed and the blood sample has been reinfused into the patient 18, additional infusion fluid drawn from fluid source 28 proceeds through both infusion line 22 and sensor assembly 12 and back into the 30 patient. Control unit 26 continues the flow of infusion fluid until a purge volume of fluid, roughly eight to ten times that of the drawn blood, has passed through the sensor assembly. This takes approximately two minutes. Thus, the control unit allows measurements to be taken as 35 frequently as at approximately two minute intervals.

It should be appreciated that the present invention provides an easily prepared calibration solution that allows for the simultaneous calibration of both gaseous and non-gaseous species in physiological fluid. The control unit of a combined infusion fluid delivery and blood chemistry analysis system employed in accordance with the present invention ensures that the fluid flow rate through the sensor assembly is approximately the same during calibration and during measurement. This eliminates the effect of fluid flow and turbulence on the measurements.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A method for the calibration of a sensor employed for the detection of CO_2 partial pressure (pCO_2), and optionally, O_2 partial pressure (pO_2), in physiological fluid, said method comprising

5 contacting a sensor assembly having:

a fluid passageway and a sensor for pCO_2 , and optionally a sensor for pO_2 , exposed to said fluid passageway, and means to pass physiological fluid and/or calibrant over said sensor,

10 with an infusion medium/calibrant comprising: physiological sodium chloride-containing saline, and

an amount of a suitable carbon dioxide

15 source effective to provide a stable pCO_2 in the range of about 1 up to 100 mm Hg, and optionally a stable pO_2 in the range of about 0 up to 200 mm Hg, and thereafter

20 calibrating said sensor.

2. A method according to claim 1 wherein said method further comprises the substantially simultaneous calibration of pO_2 and pCO_2 .

3. A method according to claim 1 wherein said method further comprises the calibration of one or more additional species selected from the group consisting of Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^- , pH, lactate and glucose, in addition to pCO_2 .

4. A method according to claim 3 wherein said calibration is carried out employing a multi-sensor assembly comprising a plurality of sensors which are responsive to one or more additional species selected

5 from Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^- , hydrogen ions, lactose and/or glucose, in addition to CO_2 .

5. A method according to claim 2 wherein said method further comprises the calibration of one or more additional species selected from Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^- , pH, lactate and/or glucose, in addition to pO_2 and pCO_2 .

6. A method according to claim 5 wherein said calibration is carried out employing a multi-sensor assembly comprising a plurality of sensors which are responsive to one or more additional species selected
5 from Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^- , hydrogen ions, lactose and/or glucose, in addition to O_2 and CO_2 .

7. A method according to claim 1 wherein said infusion medium/calibrant is selected from:

5 physiological sodium chloride-containing saline, further containing an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg, optionally containing one or more additional electrolytes,
10 0.9% sodium chloride containing an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg, optionally containing one or more additional electrolytes,

15 Isolyte™ brand infusible injection solution containing an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial

20

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pressure in the range of about 0 up to 200 mm Hg,

25 PlasmaLyte™ brand infusible injection solution containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

30 Ringer's injection containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg,

35 Ringer's Acetate containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg, or

40 Ringer's Lactate containing an amount of a suitable carbon dioxide source effective to provide a stable CO₂ partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O₂ partial pressure in the range of about 0 up to 200 mm Hg.

8. A method according to claim 7 wherein said infusion medium/calibrant further comprises in the range of about 10 up to 10,000 mg/L of dextrose.

9. A method according to claim 7 wherein said infusion medium/calibrant further comprises in the range of about 10 up to 50,000 IU/L sodium heparin.

10. A method according to claim 7 wherein said infusion medium/calibrant further comprises one or more non-buffering pH adjusting reagents.

11. A method according to claim 1 wherein said method further comprises passing a volume of calibrant through the fluid passageway of said sensor assembly sufficient to provide contact of fresh calibrant with 5 said sensor(s) when calibrating said sensor.

12. A method according to claim 1 wherein said method further comprises determining the time required for transport of fluid from the source container to the sensor, and correcting the calibration of said system to 5 reflect the diffusion loss of gases to which the tubing employed for delivery of infusible fluid is permeable.

13. A method according to claim 1 wherein said method further comprises compensating for changes in the pCO_2 in the calibrant by monitoring any changes in the pH and/or temperature of the calibrant and calculating the 5 resulting pCO_2 based on the pH of the calibrant.

14. A method for the assay of CO_2 partial pressure (pCO_2), and optionally O_2 partial pressure (pO_2), in physiological fluid, said method comprising contacting an assembly having:

5 a fluid passageway and a sensor for pCO_2 , and optionally a sensor for pO_2 , exposed to said fluid passageway, and means to pass physiological fluid and/or calibrant over said sensor,
10 with an infusible calibrant comprising: physiological sodium chloride-containing saline, and an amount of a suitable carbon dioxide source effective to provide a stable

15 pCO₂ in the range of about 1 up to 100 mm Hg, and optionally a stable pO₂ in the range of about 0 up to 200 mm Hg; and calibrating said pCO₂ sensor; and thereafter

20 contacting said assembly with said physiological fluid and measuring the pCO₂ in said physiological fluid.

15. In a method for the assay of pCO₂, and optionally, pO₂, in physiological fluid employing a sensor assembly, the improvement comprising using an infusible calibrant comprising:

5 physiological sodium chloride-containing saline, and an amount of a suitable carbon dioxide source effective to provide a stable pCO₂ in the range of about 1 up to 100 mm Hg, and optionally a stable pO₂ in the range of about 0 up to 200 mm Hg.

10

16. In a combination infusion delivery system and chemical analysis system having a sensor capable of determining CO₂ partial pressure (pCO₂), and optionally, a sensor capable of determining O₂ partial pressure (pO₂), 5 in physiological fluid, wherein physiological saline is employed as the infusion medium, the improvement comprising introducing an amount of a suitable carbon dioxide source into said physiological saline effective to provide a stable pCO₂ and optionally a stable pO₂ 10 adequate to calibrate said CO₂ and optionally said O₂ sensor.

17. Physiological saline solution suitable for infusion into a subject, and simultaneously suitable for calibration of sensors capable of detecting pCO₂ without introduction of CO₂ gas therein, and optionally capable of

5 detecting pO_2 without introduction of O_2 gas therein, said solution comprising:

10

physiological sodium chloride-containing saline, and an amount of a suitable carbon dioxide source effective to provide a stable pCO_2 in the range of about 1 up to 100 mm Hg, and optionally a stable pO_2 in the range of about 0 up to 200 mm Hg.

18. A solution according to claim 17 wherein said solution is simultaneously suitable for calibration of a multi-sensor assembly comprising a plurality of sensors, wherein the plurality of sensors are responsive to one or more additional species selected from Na^+ , K^+ , Ca^{++} , Mg^{++} , Cl^- , pH, pO_2 , lactate and glucose, in addition to pCO_2 .

19. A solution according to claim 17 wherein said solution is selected from:

5

10

physiological sodium chloride-containing saline, further containing an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg, optionally containing one or more additional electrolytes,

15

0.9% sodium chloride containing an amount of a suitable carbon dioxide source effective to provide a stable CO_2 partial pressure in the range of about 1 up to 100 mm Hg, and optionally a stable O_2 partial pressure in the range of about 0 up to 200 mm Hg, optionally containing one or more additional electrolytes,

Isolyte[™] brand infusible injection solution containing an amount of a suitable carbon

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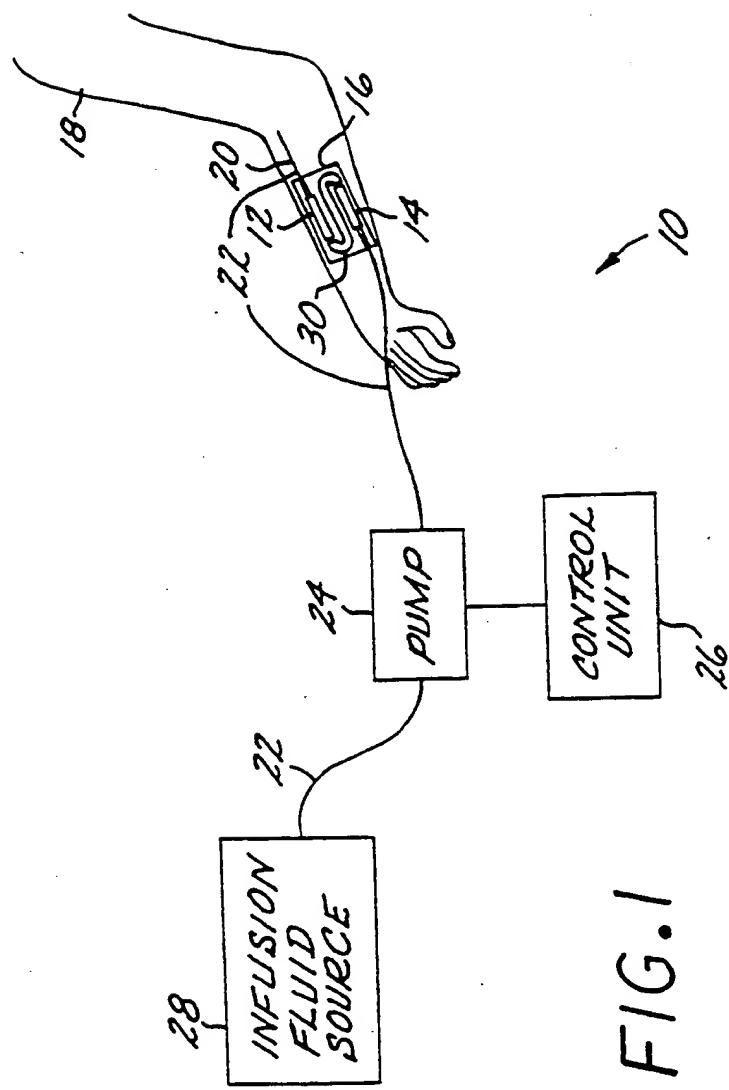
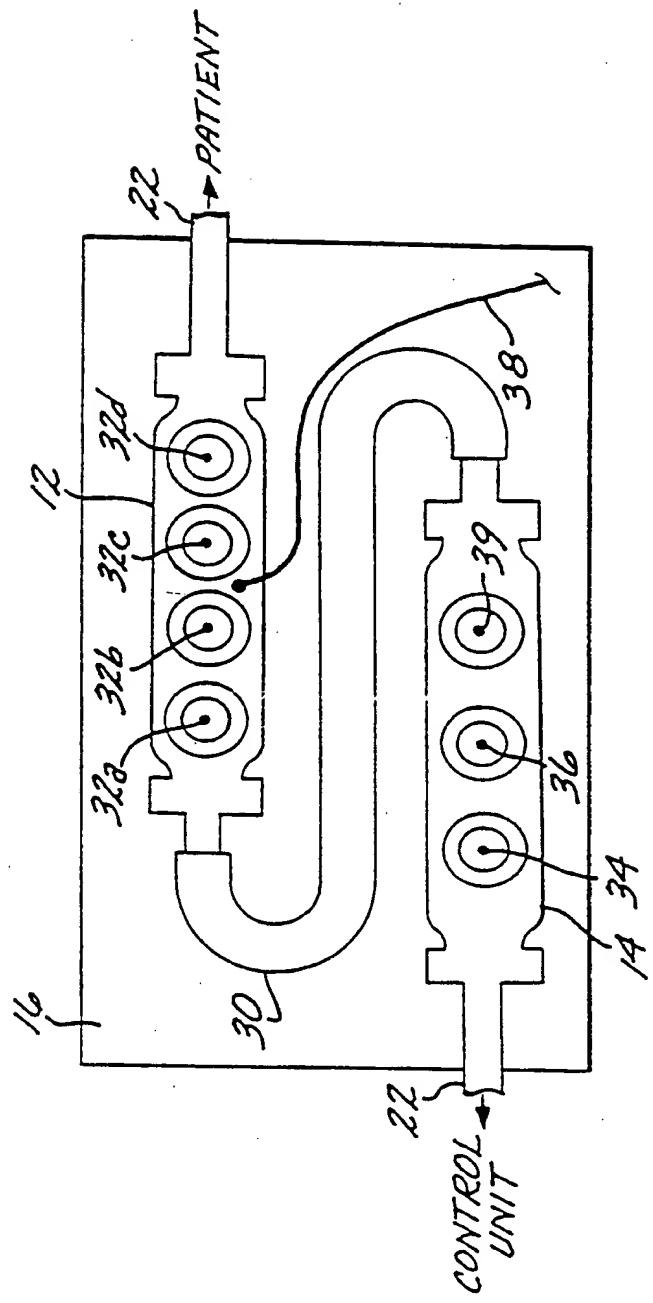


FIG. 1

SUBSTITUTE SHEET

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FIG. 2

**SUBSTITUTE SHEET**

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 93/08109A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 G01N33/96 G01N33/84 G01N33/487

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 G01N A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP,A,0 362 032 (TERUMO KABUSHIKI KAISHA) 4 April 1990 see the whole document & US,A,5 132 000 (SONE, ATSUSHI) cited in the application ---	1-19
Y	US,A,4 736 748 (MICHIHIRO NAKAMURA; MAKOTO YANO) 12 April 1988 cited in the application see the whole document ---	1-19

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

- *&* document member of the same patent family

1 Date of the actual completion of the international search

17 December 1993

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/US 93/08109

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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